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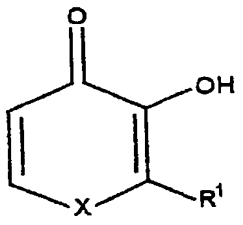

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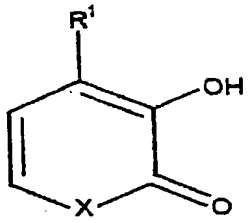

(II)

(57) Abstract: The present invention relates to a cosmetic and/or dermatological composition for the treatment and/or prevention of hyperpigmented skin which comprises at least one 3-hydroxypyr(id)one-derivative of formula (I) or (II) wherein: R^1 represents hydrogen; a linear or branched, saturated or unsaturated (C_1-C_8)-alkyl or (C_1-C_8)-alkoxy group; X represents oxygen or N-R^2; R^2 represents hydrogen; a linear or branched, saturated or unsaturated (C_1-C_8)-alkyl group, optionally substituted with (C_1-C_8)-alkoxy, carboxy, (C_1-C_8)-alcoxycarbonyl, amino, hydroxy, said amino and hydroxy being optionally (C_1-C_{22})-acylated or (C_1-C_{22})-alkylated; or a residue of an amino-acid; and salts or solvates thereof, as well as to the use of compounds of formula (I) or (II) and a method of treatment or prevention of hyperpigmented skin.

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"DEPIGMENTING COMPOSITIONS"

FIELD OF THE INVENTION

The present invention relates to new cosmetic or dermatological compositions comprising 3-hydroxy-pyrone- or 3-hydroxy-pyridone-derivatives for depigmenting human skin.

Moreover, the invention relates to the use of -3-hydroxy-pyrone- or 3-hydroxy-pyridone-derivatives for the treatment or prevention of hyperpigmentated skin.

BACKGROUND OF THE INVENTION

Skin hyperpigmentation may arise from a variety of aetiologies, including the local hyperpigmentation deriving from drug use (e.g. Ca-antagonists), the cyanic melasma, the senile melasma, the adverse sequelae following sclerotherapy, the post-inflammatory or the traumatic responses. Other local hyperpigmentations can occur during pregnancy (known as gravidic chloasma), after estro-progestative contraception, by photosensibilization and post-lesional cicatrization.

A high pigmented skin may be even considered an unaestheticisms for some individuals belonging to ethnic groups, who may aim to reduce the usual skin colour. In fact, the first depigmenting cream appeared in Korea about 50 years ago, corresponding to the aesthetic need of the Asian women to exhibit a pale facial complexion. These creams contained a mercury compound, whose action was based on the substitution of copper, essential cofactor of the tyrosinase enzyme. Mercurials were actually banned due to their neurotoxicity.

Other depigmenting agents used in the past were peroxides, such as hydrogen peroxide, zinc peroxide, sodium peroxide, benzoyl peroxide and the like.

Nonetheless, their activity is often coupled with side-effects, which renders hazardous their use.

Several natural compounds used nowadays partially inhibit the melanin synthesis and/or the tyrosinase activity, for example glucosamines, galactosamines, mannosamines, and some vegetal extracts, whose action is probably due to the blockade of the free radicals which are the actual stimulating factors of melanogenesis.

Further antioxidants such as vitamin C and E and esters thereof exhibit moderate depigmenting activity, with partial inhibition of melanogenesis, however they are often not effective enough to cope with the requested aesthetical purposes.

Azelaic acid had been introduced as anti-acne treatment in Azelex® (Allergan, Irvine, USA), used as depigmenting agent since it demonstrated a competitive inhibition of tyrosinase and of the DNA synthesis within melanocytes.

Hydroquinone and its derivatives, such as the monomethyl ether hydroquinone and arbutin, are the most common depigmenting agents in topical compositions. Prescription skin lightening agents may contain between 3 and 5% hydroquinone, however the dosage should be limited to a concentration of 2%, as hydroquinone is irritating and cytotoxic to the melanocyte, with records of localized granular hyperpigmentation and formation of elastosis (Sylla R et al, Dakar Med., 3, 223-6, 1994) as well as the occurrence of vitiligo by its long-term use.

Hydroquinone is a tyrosinase substrate with antagonist and competitive action on tyrosine, being frequently associated with the espholiating alpha hydroxyacids (AHA).

Particularly, low molecular weight AHA has been successfully used to enhance the action of known dipigmentating agents, such as the combination of

glycolic acid with hydroquinone (Lim JT, Tham SN Dermatol Surg, 23 (3): 177-179, 1997), with tretinoin (Lawrence N, Cox SE, Brody HJ, J. Am. Acad. Dermatol., 36 (4): 589-93, 1997), or with kojic acid (Garcia A, Fulton JE, Dermatol Surg, 22(5): 443-7, 1996).

However, also the use of kojic acid brings about skin irritation and chronic hypocromias (Iurassich S, Santoro M, Rossi E, G. Ital. Venereol., 132:443-4, 1997).

A particular hyperpergmentative condition refers to the postsclerotherapy sequelae, wherein some degree of cutaneous hyperpigmentation is a relatively common occurrence after sclerotherapy of veins, varying from capillary to varicoses. The formation of pigmentary spots may result from the combination of blood extravasation around the injection site and the melanic hyperactivity related to the inflammatory process promoted by the extravasation thereof.

Hemoglobin is promptly bounded to the dermal and connective proteins, thus forming hemosiderin deposits, which in turns may stimulate the activity of the surrounding melanocytes.

The same condition of pigmentative hemosiderin deposition and incontinence of melanin production may also occur following the treatment of follicolosis and after the subcutaneous injection of tattoos. Particularly, in tattooing the hyperpigmentation results may arise from the multiple combination of postinflammatory hemosiderinic deposits, melanin overexpression, pigment deposition and/or thermic shock.

Similar phenomena may also occur after episodes of traumas with ematomas, where again the blood extravasation is sometimes combined with the overstimulation of melanocytes, thus secreting melaninosomes and/or extracellular melanin.

Besides the expensive treatment with laser, which may cause permanent scars

on skin, so far no chemical substances and related methods of use have given satisfactory results on the aforementioned pigmentative unaestheticisms.

The treatment of hemosiderinic as well as melanic spots have been tentatively carried out by esfoliating agents (e.g. by trichloroacetic acid), or by the cryotherapy, or by the use of retinoic acid.

Several attempts have been made to perform the iron chelation in skin hemosiderosis, for example by the application of creams containing EDTA or by the intradermic injection of the oral chelator desferoxamine, all apparently with poor results.

A new oral iron chelator, namely deferiprone, is a 3-hydroxy-4-pyridinone, which was recently launched in the pharmaceutical market for the treatment of the iron overloading, such as in transfusion dependent beta-hemoglobiopathies, e.g. thalassemia major and sickle cell anaemia.

With the aim to evaluate the lack of toxicity by the oral intake, deferiprone was tested for its possible ability to inhibit tyrosinase and thereby compared with reference tyrosinase inhibitors, as illustrated by the Hider et al. in Biochem J. 257, 289-290 (1989). This work pointed out that members of the same chemical family, namely compounds having similar chemical structure of deferiprone, do not show an homogeneous biochemical behaviour but exert a variety of different inhibitory effects on tyrosinase, some of them being rather inactive in the assay performed by the authors.

Also, it is clear from the above that to date, there is no effective treatment for skin hyperpigmentation due to both an excess in melanin synthesis and hemosiderinic deposits.

DESCRIPTION OF THE INVENTION

A depigmenting agent shall act on the epidermic melanocytes by the inhibition of one of the steps in the biosynthesis of melanins, i.e. either by inhibiting or antagonising the melanogenesis enzymes. Preferably a depigmenting agent should also be active in removing skin hemosiderin deposits which are frequently associated with hypermelanosis.

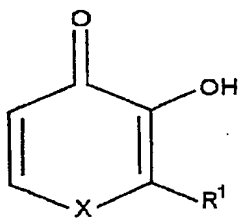
We have now surprisingly found out that 3-hydroxypy(id)one-derivatives can significantly treat skin hyperpigmentative disorders.

In our findings, substances such as 3-hydroxypy(id)one-derivatives represent the ideal depigmenting agents to be applied on hyperpigmented skin, as they show a combined activity towards melanin and/or hemosiderin deposits.

It is to be noticed that the present invention is addressed to the depigmentation (also called whitening) of "hyperpigmented skin" wherein said expression refers to skin impairments showing spots, or larger areas of a dark colour, either due to an excess of melanin and/or to hemosiderinic deposits. Hyperpigmented skin in fact is often the result of this two occurrences and it is therefore important to provide a treatment which is effective on both impairements.

One of the aim of the present invention is to provide an effective treatment of hyperpigmented skin, which can not only treat or prevent melanin spots of different origin but, where necessary, also reduce and/or completely whiten hemosiderin spots.

Therefore, according to one of its aspects, the present invention concerns a cosmetic and/or dermatological composition for the treatment and/or prevention of hyperpigmented skin which comprises at least one 3-hydroxypyr(id)one-derivative of formula (I) or (II):



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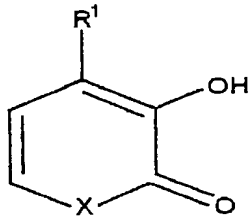


(II)

wherein:

R^1 represents hydrogen; a linear or branched, saturated or unsaturated (C_1-C_8)- alkyl or (C_1-C_8)-alkoxy group;

X represents oxygen or N-R^2;

R^2 represents hydrogen; a linear or branched, saturated or unsaturated (C_1-C_8)-alkyl group, optionally substituted with (C_1-C_8)-alkoxy, carboxy, (C_1-C_8)-alcoxycarbonyl, amino, hydroxy, said amino and hydroxy being optionally (C_1-C_{22})-acylated or (C_1-C_{22})-alkylated; or a residue of an amino-acid;

and salts or solvates thereof.

The group N-R^2 may thus represents an aliphatic hydroxyamine, such as 2-hydroxyethylamine, or 3-hydroxypropylamine; or a diamine, such as ethylenediamine; or an amino acid, such as glycine, alpha- or beta-alanine, gamma-aminobutyric acid or taurine.

The "(C_1-C_{22})-acylated" and "(C_1-C_{22})-alkylated" expressions means linear or branched, saturated or unsaturated substituents, such as for example fatty acid residues.

Preferred compounds of formula (I) or (II) are those where R^1 and R^2 are lower alkyl groups, such as methyl, ethyl, isopropyl, or n-propyl groups.

Compounds of formula (I) and (II) are to a large extent known compounds and can be prepared by known methods whilst the other compounds can be prepared by analogous methods.

Examples of compounds of formula (I) wherein X=O which may be used in compositions of the invention are 3-hydroxy-4-pyrone (R^1=H), also called pyromeconic acid; 3-hydroxy-2-methyl-4-pyrone (R^1=CH_3), also called maltol or larixinic acid; and 3-hydroxy-2-ethyl-4-pyrone (R^1=C_2H_5) also called ethyl maltol or ethylpyromeconic acid.

Certain 3-hydroxy-4-pyrones are commercially available, including maltol and ethyl maltol, both being widespreadly used as flavouring and fragrance-enhancing agents for foods. Maltol is a naturally occurring substance which may be either synthetized, as illustrated by Fung et al. in US5908941, or obtained by extraction from the natural sources, e.g. from the bark of the young larch tree, pine needles, chicory, wood tars and oils, and roasted malt.

Synthesis of gamma-pyrones such as pyromeconic acid, maltol, ethyl maltol and other 2-substituted-3-hydroxy-gamma-pyrones are described for instance in US3130204, 3133089, 3140239, 3159652, 3365469, 3376317, 3468915, 3440183, 3446629, 4082717, 4147705, 4323506, 4342697, 4387235, 4390709, 4435584, 4451661, and US4435584.

The 3-hydroxy-2-pyridone derivatives may conveniently be prepared by nucleophilic substitution of the nitrogen atom of the corresponding 2,3-dihydroxypyridine with an alkylating agent, for example using an organic halide of formula R^2X in which X is an halogen group.

The 3-hydroxy-4-pyridone compounds may conveniently be similarly prepared or preferably from the more readily accessible corresponding 3-hydroxy-4-

pyrone. Thus, the 3-hydroxy-4-pyrone may conveniently be converted to the 3-hydroxy-4-pyridone through protection of the hydroxy groups, for example as an ether group such as a benzyloxy group, reaction of the protected compound with a compound R^2NH_2, in the presence of a base, for example an alkali metal hydroxide such as sodium hydroxide. The hydroxy protecting group may then be removed and any other modifications of the C-substituents effected.

Other methods to produce substituted 3-hydroxy-4- and 2-pyridones may be conveniently applied, such as those described by Hider et al. in USRE35948.

According to another of its aspects, the present invention concerns the use of the compounds of formula (I) or (II) or a salt thereof, for the treatment of hyperpigmented skin.

The particular ability of the 3-hydroxypy(id)one-derivatives to both inhibit endogenous melanin production and to remove hemosiderin spots, makes the compounds be particularly useful in whitening or depigmenting the skin, also in such cases where no specific evaluation of the origin of the hyperpigmentation is made.

Accordingly, the compounds and the composition of the present invention can be useful for treating all sort of skin pigmentation, for instance they can be useful for depigmenting melasma, i.e. dark patches of pigmentation of the face and of other part of the body, or for voluntary whitening skin physiological pigmentation, as well as for whitening spots due to iron deposit (hemosiderinic pigmentation), all those treatments being possible to concomitantly occur.

In order to exploit the cosmetic treatment of the invention the compounds of formula (I) or (II) are preferably administered in the form of a topical composition, said composition having a content of 3-hydroxypy(id)one-derivative from 0.01 to

50% by weight, preferably from 0.1 to 20% by weight, more preferably from 1 to 7% by weight, optionally in admixture with suitable customary auxiliary agents.

In one of the preferred embodiments of the present invention, the compounds of formula (I) or (II) are combined with one or more well-known depigmenting agent.

Illustrative examples of known depigmenting agent include kojic acid; caffeic acid; retinoic acid; hydroquinone and the derivatives thereof, such as benzylhydroquinone ether; ascorbic acid and the derivatives thereof, such as magnesium ascorbyl phosphate; hydroxycinnamic and caffeic acids and esters thereof, benzofurans such as 5- or 6-hydroxybenzofuran, extracts of plants such as licorice, mulberry, heather and angelica ashitaba; pearl extracts; steroidal anti-inflammatory agents of hydrocortisone type and the like; nonsteroidal anti-inflammatory agents selected from the group consisting of aspirin (acetylsalicylic acid), acetaminophen, naproxen and fenamic acid derivatives such as the sodium salt; anti-inflammatory agents include, but are not limited to, alphabisabolol, beta-glycyrrhetinic acid, allantoin, aloe extract, rosmarinic acid, azulene and derivatives thereof, asiaticoside, sericoside, ruscogenin, escin, escolin, quercetin, rutin, betulinic acid and derivatives thereof, catechin and derivatives thereof. an well as mixtures of these active agents. These anti-inflammatory agents promote depigmentation of the skin, in particular when they are associated with a depigmenting or anti-pigmenting agent.

According to another of its aspects, the present invention relates to a method for the prevention and/or treatment of hyperpigmented skin which comprises topically administering to the affected skin areas at least a compound of formula (I) or (II) or a salt thereof.

The compounds of formula (I) or (II) used in the method of the present invention are most preferably applied in the form of appropriate cosmetic or dermatological compositions, in particular compositions usually employed for the administration of active ingredients on human skin.

Suitable compositions contain the active ingredient and a skin-acceptable carrier. They may take a wide variety of forms such as, for example, solid forms, e.g. powders; liquid forms, e.g. solutions, gelled solutions or suspensions in aqueous or oily mediums; semi-liquid formulations, e.g. creams, gellies, pastes, ointments, salves, liposomes, microemulsion and nanospheres comprising as the active principle as well as suitable carriers.

The composition according to the invention may also comprise any cosmetically acceptable ingredients. The expression "cosmetically acceptable ingredients" designate in the present specification products which are suitable for their use in cosmetic treatments, for example those included in the INCI list drawn by the European Cosmetic Toiletry and Perfumery Association (COLIPA) and issued in 96/335/EC "Annex to Commission Decision of 8 May 1996" and further modifications.

A variety of active ingredients may further be added to the composition according to the present invention. Although not limited to this category, general examples include UV-filters, antioxidants and anti-wrinkling agents.

Besides the above-described compositions, use may be made of covers, e.g. plasters, bandages, dressings, gauze pads and the like, containing an appropriate amount of a composition as referred hereinabove. In some cases use may be made of plasters, bandages, dressings, gauze pads and the like which have been impregnated or sprinkled with a liquid formulation containing the active agent, e.g. with an

aseptic aqueous solution, or strewed with a powdery solid composition, or smeared, covered or coated with a semi-liquid composition.

According to a further preferred embodiment of the invention, the compositions comprise one or more esfoliating agent.

A preferred esfoliating agent is trichloroacetic acid or an alpha hydroxy acid (AHA), which facilitates the opening of the stratum corneum and the structure of dermal tissue, thus facilitating the penetration and activity of the compounds of formula (I) or (II).

The above mentioned AHA has the following general structure:

$$R^3CHOHCOOR^4$$

wherein R^3 and R^4 are H, or (C_1-C_{20})alkyl, arylalkyl or aryl, said alkyl having a straight or branched chain or a cyclic form, and in addition R^4 may carry OH, CHO, COOH and (C_1-C_9)alkoxy group.

Typical alkyl, aralkyl and aryl groups include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl, etc.

The preferred AHAs are monocarboxylic acids, in order to improve skin penetration and efficacy. Even more preferably, the AHA is chosen in the group consisting of lactic acid, glycolic acid, salicylic acid and mandelic acid, and mixtures thereof to optimize the efficacy of compositions by increasing percutaneous absorption.

Preferably, a suitable composition for the aforementioned administration comprises one or more esfoliating agent in a quantity comprised from 5% to 80%, more preferably from 10% to 70% by weight of the composition.

Depending on the type of the treatment, such as for instance the administration route or the proportion of esfoliating agents in the composition, the

method of the invention may be self-performed by the subject affected by the hyperpigmentation or alternatively performed by a professional cosmetologist. By way of example, the compositions comprising the compounds of formula (I) or (II) and with a content of esfoliating agent from 30 to 80% are preferably administered by a professional cosmetologist or beautician or aesthetic dermatologist who can carefully monitoring the correct procedure for the peeling treatment.

On the other side, compositions comprising the compounds of formula (I) or (II) and with a content of esfoliating agent of from 0 to 30% my be self administered by the subject bearing the hyperpigmentation spot.

According to another embodiment, the active ingredient of formula (I) or (II) may also be applied by iontophoresis or by local injection, e.g. syringe or dermojet. In the latter modes of application the compositions will conveniently be in a sterilized liquid formulation comprising the compounds of formula (I) or (II). For a delivery based on iontophoresis use, liquid formulations containing the active ingredients of formula (I) or (II) may be used. When such a dermal injection or iontophoresis administration are needed or desired, the method of the invention must always be carried out by a skilled professional.

Other compositions are preparations of the cosmetic type, such as toilet waters, packs, lotions, skin milks or milky lotions. Thus, said preparations may contain, besides the active ingredient, components usually employed in such preparations, examples of such components being oils, fats, waxes, surfactants, humectants, thickening agents, antioxidants, viscosity stabilizers, chelating agents, buffers, preservatives, perfumes, dyestuffs, lower alkanols. If desired, further ingredients may be incorporated in the compositions, e.g. anti-inflammatory agents,

antibacterials, antifungals, disinfectants, vitamins, sunscreens, anti-acne agents, antibiotics, etc.

Examples of oils comprise fats and oils such as olive oil, and hydrogenated oils; waxes such as beeswax and lanolin; hydrocarbons such as liquid paraffin, ceresin, and squalane; fatty acids such as stearic acid and oleic acid; alcohols such as cetyl alcohol, stearyl alcohol, lanolin alcohol, and hexadecanol; and esters such as isopropyl myristate, isopropyl palmitate and butyl stearate. As examples of surfactants there may be cited anionic surfactants such as sodium stearate, sodium cetylsulfate, polyoxyethylene laurylether phosphate, sodium N-acyl glutamate; cationic surfactants such as stearyldimethylbenzylammonium chloride and stearyltrimethylammonium chloride; ampholytic surfactants such as alkylaminoethylglycine hydrochloride solutions and lecithin; and nonionic surfactants such as glycerin monostearate, sorbitan monostearate, sucrose fatty acid esters, propylene glycol monostearate, polyoxyethylene oleylether, polyethylene glycol monostearate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene coconut fatty acid monoethanolamide, polyoxyethylene polyoxypropylene glycol, polyoxyethylene castor oil, and polyoxyethylene lanolin. Examples of humectants include glycerin, 1,3-butylene glycol, and propylene glycol; examples of lower alcohols include ethanol and isopropanol; examples of thickening agents include xanthan gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene glycol and sodium carboxymethyl cellulose; examples of antioxidants comprise butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate and citric acid ethoxyquin; examples of chelating agents include disodium edetate and ethanehydroxy diphosphate; examples of buffers comprise citric acid, sodium citrate, boric acid, borax, and disodium hydrogen phosphate; and examples of preservatives

are methyl parahydroxybenzoate, ethyl parahydroxybenzoate, dehydroacetic acid, salicylic acid and benzoic acid.

For preparing ointments, creams, lotions, milks, and the like, typically from 0.1 to 20%, in particular from 1 to 7% of the compounds of formula (I) or (II) is used. In ointments or creams, the carrier for example consists of 1 to 20%, in particular 5 to 15% of a humectant, 0.1 to 10% in particular from 0.5 to 5% of a thickener and water, or said carrier may consist of 70 to 99%, in particular 20 to 95% of a surfactant, and 0 to 20%, in particular 2.5 to 15% of a fat; or 80 to 99.9% in particular 90 to 99% of a thickener; or 5 to 15% of a surfactant, 2-15% of a humectant, 0 to 80% of an oil, very small (<2%) amounts of preservative, colouring agent and/or perfume, and water. In a lotion, the carrier for example consists of 2 to 10% of a lower alcohol, 0.1 to 10% or in particular 0.5 to 1% of a surfactant, 1 to 20%, in particular 3 to 7% of a humectant, 0 to 5% of a buffer, water and small amounts (<2%) of preservative, dyestuff and/or perfume. In a milk, the carrier typically consists of 10-50% of oil, 1 to 10% of surfactant, 50-80% of water and 0 to 3% of preservative and/or perfume. In the afore-mentioned preparations, any % refers to a % by weight.

The humectant, surfactant, oil, etc. referred to in said preparations may be any such component used in the cosmetic arts but preferably will be one or more of the aforementioned components. Further, when in the above compositions one or more of the components make up the major part of the composition, the other ingredients can evidently be not present at their indicated maximum concentration and therefore will make up the remainder of the composition.

Particular compositions for use in the method of the present invention are those compositions wherein the compounds of formula (I) or (II) are formulated in liposome containing compositions, according to the well known techniques.

Water-soluble active ingredients such as, for example, most of the salt forms of the deanol and its derivatives are encapsulated in the aqueous spaces between the molecular layers. Lipid soluble active ingredients, e.g. most of the base forms of the deanol and its derivatives, are incorporated into the lipid layers, although polar head groups may protrude from the layer into the aqueous space. The encapsulation of these compounds can be achieved by known methods. In some particular cases, it may be advantageous to use micronized forms of the active ingredient, i.e., material having an average particle size of less than 10 microns, as the high surface area will facilitate the dissolution of the liposomal components.

For the intended treatment, the compositions of the invention are administered 2 to 4 times per day, preferably 1 to 3 times, advantageously at least 2 times per day.

In order to perform the treatment of the invention, the composition is applied on the skin, preferably with soft massage to enhance the penetration of the cosmetic active ingredients.

The following examples are intended to illustrate the scope of the present invention but not to limit it.

Preparative Examples A1, A2, A3 B1, C1 – Synthesis of compounds of formula (I) with $X=N-R^2$

Compounds of formula (I) with a substituted nitrogen atom may be synthesized according to one of several general procedures.

Method A

This procedure is adapted from Kontoghiorghes and Sheppard in Inorg. Chim. Acta 136:L11-L12 (1987), optionally with minor modifications as described by Zhang et al., in Can. J. Chem. 70:763-770 (1992). Briefly, a 3-hydroxy-4-pyrone is refluxed for approximately 6 hours with three equivalents of a primary amine dissolved in an appropriate solvent. The reaction mixture is decolorized with charcoal, filtered, and the filtrate evaporated to give a dark residue. The residue is recrystallized from one to three times from an appropriate solvent to yield a solid product.

A1) 1,2-dimethyl-3-hydroxy-4-pyridone

10 g of 3-hydroxy-2-methyl-4-pyrone were refluxed for 6.5 hours with three equivalents of aqueous methylamine (40%) in 200 ml of water. The reaction mixture was allowed to cool after which decolorizing charcoal was added to the solution, and the mixture was stirred for 0.5 hours. After filtration, the solvent was evaporated under reduced pressure, and the solid residue recrystallized three times from water to yield 1,2-dimethyl-3-hydroxy-4-pyridone (deferiprone) as fine white needles.

A2) N-carboxymethyl-3-hydroxy-2-methyl-4-pyridone

One equivalent of 3-hydroxy-2-methyl-4-pyrone and two equivalents of glycine are dissolved in hot distilled water, the pH is adjusted to approximately 9 with NaOH 10N, and the reaction mixture is heated under reflux for 20 hours. After cooling and decolorizing with charcoal, approximately half of the solvent is removed under vacuum and 6N hydrochloric acid is added to reduce the pH to approximately 3. A yellow solid precipitates which yields the product as off-white crystals after two recrystallizations from water (mp 258°-260° C.).

A3) N-methyl-3-hydroxy-4-pyridone

10 g of pyromeconic acid were refluxed for 6.5 hours with three equivalents of aqueous methylamine (40%) in 200 ml of water and the reaction mixture was treated as in Example A1 to yield 1-methyl-3-hydroxy-4-pyridone as fine white needles.

Method B

This method is adapted from GB2118176 by Hider et al. In brief, a 3-hydroxy-4-pyrone is converted to the corresponding 3-benzyloxy-4-pyrone via reaction with benzyl chloride. A methanolic solution of the pyrone is added to an aqueous solution of sodium hydroxide after which benzyl chloride is added and the reaction mixture refluxed for approximately 6 hours. The solvent is evaporated under reduced pressure, water is added, and then the product is extracted into chloroform. After washing, the extract is dried over anhydrous magnesium sulfate and the solvent evaporated to yield the crude 3-benzyloxy derivative which is used in the next step without further purification. To a solution of the 3-benzyloxy compound in an chloroform is added a slight excess of primary amine. The reaction mixture is stirred at room temperature for approximately 6 days after which it is acidified to pH 2 with HCl and evaporated to dryness. The residue is washed with water and extracted into an appropriate organic solvent which is then dried over magnesium sulfate and evaporated to dryness. To the residue is added hydrobromic acid. This reaction mixture is heated on a steam bath for 30 minutes and then recrystallized from water to yield the N-substituted 3-hydroxy-4-pyridone.

B1) 2-ethyl-3-hydroxy-1-methyl-4-pyridone

2-ethyl-3-hydroxy-4-pyrone (24.7 g) in 225 ml of methanol is added to of NaOH 10N. To this solution benzyl chloride (25.5 g) is added and the mixture is then refluxed for 6 hours. Upon cooling, the solvent is removed under reduced pressure. The residue is treated with 50 ml of water and then extracted three times with 25-ml

aliquots of dichloromethane. The combined extracts are washed twice with 50% (w/v) NaOH, then twice with 25 ml of water and dried over magnesium sulfate. Evaporation of the solvent yields crude 3-benzyloxy-2-ethyl-4-pyrone. This crude pyrone (24.4 g) and 1.56 g of methylamine hydrochloride are then dissolved in 300 ml of aqueous ethanol (100 ml) containing 2 g of NaOH. The solution is stirred at room temperature for 6 days, acidified to pH 2 with HCl, and then evaporated to dryness. The residue is washed with water and extracted twice into chloroform (50 ml). The combined extracts are dried over anhydrous magnesium sulfate and evaporated to dryness yielding 3-benzyloxy-2-ethyl-1-methyl-4-pyridone. To 2 g of this -4-pyridone concentrated hydrobromic acid (10 ml) is added. The reaction mixture is heated on a steam bath for 30 minutes, and the product is recrystallized from water to yield 2-ethyl-3-hydroxy-1-methyl-4-pyridone.

Method C

This method is adapted from that of Bartulin et al., J. Heterocyclic Chem. 29:1017-1019 (1992). A 3-benzyloxy-4-pyrone, prepared as in Method B, is added to an ethanolic solution of aqueous ammonia. The reaction mixture is stirred for approximately 3 days, concentrated under reduced pressure, triturated with acetone, and the solid recrystallized from ethanol to yield the corresponding 3-benzyloxy-4-pyridone. To a solution of this -4-pyridone in aqueous ethanol containing one equivalent of NaOH an equivalent of n-alkyl bromide was added. The reaction mixture was heated under reflux for 24 hours after which it was cooled, concentrated under reduced pressure, and extracted with an appropriate solvent. After washing, the organic phase with water, it is dried over magnesium sulfate. The product is obtained upon concentration of the solution under reduced pressure. Crude 1-alkyl-3-benzyloxy-4-pyridone in acetic acid containing 40% HBr is then heated for 30

minutes. The 1-alkyl-3-hydroxy-4-pyridone precipitates and is subsequently recrystallized from benzene in good yield.

C1) 1-hexyl-3-hydroxy-2-methyl-4-pyridone

3-benzyloxy-2-methyl-4-pyrone was prepared as described in Method B. A solution containing 15.3 g of the pyrone, 160 ml of aqueous ammonia (25%), and 80 ml of ethanol is stirred at room temperature for 3 days. The solvent is removed under reduced pressure and some acetone is added. The solid which precipitates is collected by filtration and recrystallized from ethanol to yield (80%) 3-benzyloxy-2-methyl-4-pyridone with a melting point of 162°-163° C. A solution containing 0.125 moles of the -4-pyridone, 0.125 moles of n-hexyl bromide, 0.125 moles of sodium hydroxide, 25 ml of water, and 200 ml of ethanol is heated under reflux for 24 hours. After removal of the solvent under vacuum, the residue is extracted with ethyl ether. The etherial solution is washed with water yielding a precipitate which is crystallized from benzene after drying to give 3-benzyloxy-1-hexyl-2-methyl-4-pyridone (95%, mp 46° C). A solution of this compound in 80 ml of acetic acid containing 40% HBr is then heated on a steam bath for 30 minutes. The product is filtered off and crystallized from benzene to yield 1-hexyl-3-hydroxy-2-methyl-4-pyridone in 70% yield.

Preparative Example D1, D2 – Synthesis of compounds of formula (II) with X = N-R^2

Compounds of formula (II) with a substituted nitrogen atom are synthesized by the method D, as outlined in GB1118176 by Hider et al..

Method D

Briefly, 2,3-dihydroxypyridine is mixed with an organic halide in a sealed tube and heated at 140° C for 24 hours. The tube is then cooled in an acetone/dry ice bath and

opened. The excess halide is poured off, and water is added to the dark residue. Sulfur dioxide gas is bubbled through the mixture until the aqueous phase becomes clear. The pH of the reaction mixture is then adjusted to approximately 6 with sodium carbonate, and the resulting solution is extracted with an appropriate solvent after saturation with ammonium sulfate. The organic extracts are dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield a solid which gives the desired N-substituted 3-hydroxy-2-pyridone after crystallization from petroleum ether.

D1) 3-hydroxy-1-methyl-2-pyridone

5.6 g of 2,3-dihydroxypyridine in 20 ml of methyl iodide are heated in a sealed tube at 140° C for 24 hours. The tube is cooled in acetone/dry ice, opened, and the excess methyl iodide poured off. Distilled water (10 ml) is added, and the solution is treated with sulfur dioxide until clear. The pH of the reaction mixture is adjusted to 6 with aqueous sodium carbonate (1M) after which the resulting solution is saturated with ammonium sulfate followed by extraction with chloroform until the chloroform layer fails to give a blue color with aqueous ferric chloride. The combined extracts are dried over sodium sulfate after which the solvent is removed under reduced pressure and the residue crystallized from petroleum ether to give 3-hydroxy-1-methyl-2-pyridone.

D2) 1-ethoxycarbonylmethyl-3-hydroxy-2-pyridone

A mixture of 2,3-dihydroxypyridine (5 g) and 20 ml of ethylbromoacetate is heated in a sealed tube at 140° C for 24 hours, as described by GB4585780 by Hider et al. After cooling in solid CO_2, the tube is opened, the reaction mixture poured off, and evaporated to dryness under vacuum to yield a yellow solid. Recrystallization from water yields the product as white crystals (5.4 g), mp 141°-151° C.

Applicative Example 1 – Skin lightning o/w cream for indoor use (home treatment)

100 g of o/w cream contain:	
mineral oil	4.0 g
3-hydroxy-1-methyl-2-pyridone	2.0 g
cetyl ether-(10)-POE	4.0 g
cetyl alcohol	4.0 g
triethanolamine	0.75 g
butane-1,3-diol	3.0 g
xanthan gum	0.3 g
BHT	0.01g
perfume	0.3 g
distilled water	qb to 100 g

Applicative Example 2 – Skin lightning protected cream for daylight (home treatment)

100 g of suncare contain:	
beta-Carotene	0.01 g
pyromeconic acid	2.1 g
silicone oil 200 cts	7.5 g
glycerylmonostearate	3.0 g
cetosteryl alcohol	1.6 g
cetyl alcohol (20)-POE	1.4 g
xanthan gum	0.5 g
octyl methoxycinnate	3.0 g
perfume	0.2 g

color	0.1 g
distilled water	qb to 100 g

Applicative Example 3 - Skin lightning lotion for melasmas on limbs (home treatment)

100 g of o/w alcoholic lotion contain:

tocopheryl acetate	0.15 g
deferiprone	5.0 g
perfume	0.3 g
BHT	0.01 g
ethyl alcohol 45° v/v	qb to 100 g

Applicative Example 4 - Skin lightning summer face cream (extended home treatment)

100 g of protective day face cream contain:

stearine	1.75 g
maltol	1.05 g
1-hexyl-3-hydroxy-4-pyridone	1.40 g
propyleneglycol monostearate	2.7 g
isopropyl lanolate	3.5 g
bentone gel of propylene glycol caprate and caprylate	6.0 g
isopropyl palmitate	6.5 g
silicone oil	3.0 g
sorbitan stearate	1.8 g

polyoxyethylenated sorbitanstearate	1.5 g
cetyl alcohol	0.6 g
UVA and UVB filters	2.0 g
tetrasodium EDTA	0.1 g
aluminium silicate	0.8 g
carboxymethylcellulose	0.15 g
propylene glycol	4.0 g
preservatives	0.5 g
perfume	0.35 g
distilled water	qb to 100 g

Applicative Example 5 - Skin lightning non-aqueous skin care (home treatment)

100 g of non-aqueous skin care contain:

retinoic acid	0.15 g
1-hexyl-3-hydroxy-2-methyl -4-pyridone	1.5 g
arbutine	1.30 g
squalene	9.0 g
linoleic acid	0.01 g
cholesterol	0.03 g
2-hydroxy-n-octanoic acid	0.7 g
herbal oil	0.5 g
ethanol	2.0 g
silicone gum SE-30 (1)	10.0 g
silicone fluid 345 (2)	18.0 g

silicone fluid 344 (3)	qb to 100 g

(1) a dimethyl silicone polymer having a molecular weight of at least 50,000 and a viscosity of at least 10,000 centistokes at 25° C, available from GEC;

(2) Dimethyl siloxane cyclic pentamer, available from Dow Corning Corp;

(3) Dimethyl siloxane tetramer, available from Dow Corning Corp.

Example 1 – Dermal patch for bleaching hyperpigmented (ethnical) skin .

Each mass for dermal patch contains:

	patch (A)	patch (B)	patch (C)
2-methyl-3-hydroxy-4-pyrone (maltol)	2 g	-	-
1,2-dimethyl-3-hydroxy-4-pyridone (deferiprone)	-	2 g	-
1-methyl-3-hydroxy-4-pyridone	-	-	2 g
lactose	30 g	30 g	30 g
saturated triglycerides	2 g	2 g	2 g
polyisobuthene	22 g	22 g	22 g
hydrogenated colofonia	17,5 g	17,5 g	17,5 g
polyalkadiene	26,5 g	26,5 g	26,5 g

The adhesive film is spread on a sheet and a coverage bandage, thus obtaining patches which release the depigmenting agents during 24 hours.

Assay

3 subjects of the afro ethnic group (country of origin: Senegal) are provided with 12x12 cm of each patch A, B, and C, then instructed to apply a new patches every day. After 1 month of treatment, the subjects are monitored by comparison of the application areas with the color of untreated skin on the surrounding area. The results are shown in Table II.

TABLE II – Pigmentary evaluation

	Densitometry (diff. %)
patch A	-5%
patch B	-39%
patch C	-52%

As it can be observed, the preparation A is more effective then B and C, which exhibit lower activities on melanin inhibition.

Example 2 – Peeling gel for postsclerotherapy spots (home treatment)

100 g of each gel contains:

	Gel (A)	Gel (B)	Comparative Gel (A)
1-ethyl-2-methyl-3-hydroxy-4-pyridone	2 g	-	-
deferiprone	-	2 g	-
desferoxamine	-	-	2 g
glycolic acid	8 g	8 g	8 g
xanthan gum	1,2 g	1,2 g	1,2 g
distilled water qb	to 100 g	to 100 g	to 100 g

Assay

2 female subjects with a several persistant pigmentary spots on legs which have underwent sclerotherapy, were instructed to separately apply a preparation on each single hemosiderinic spot. After 3 weeks, the spots treated with Gel (A) and (B) were almost disappeared, whereas the spot treated with Comparative Gel (A) was still perceivable.

Example 3 - Peeling gel for the discoloration of tattoo marks (professional use)

100 g of each gels contain:

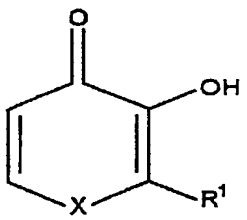
deferiprone	5.0 g
glycolic acid	70.0 g
alpha-tocopherol	0.5 g
retinoic acid	0.2 g
xanthan gum	1.2 g
aloe gel	2.0 g
deionized water	qb to 100 g

Assay

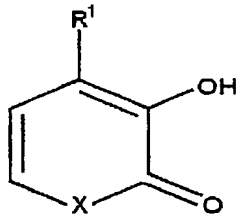
A subject ageing 24 years with a large tattoo on the left forearm and some extravasation lose to the external line of the figure were chosen for the treatment. The gel was applied on the area and let in the place for 12-13 minutes, until the skin color started to switch from red to pale complexion. At this time the application was stopped by wiping, washing with a gel of sodium bicarbonate 5%. The treatment was repeated once again but leaving the peeling gel for half of the time. The area was again neutralized and washed, and then rinsed with a gel containing aloe vera and glycirrizic acid. The treated area formed a scar, which heal up in about 2 weeks. Afterwards there were but minor signs of the previous tattoo and relevant skin marks.

CLAIMS

1. A cosmetic and/or dermatological composition for the treatment and/or prevention of hyperpigmented skin which comprises at least one 3-hydroxypyr(id)one-derivative of formula (I) or (II):



(I)



(II)

wherein:

R^1 represents hydrogen; a linear or branched, saturated or unsaturated (C_1-C_8)- alkyl or (C_1-C_8)-alkoxy group;

X represents oxygen or N-R^2;

R^2 represents hydrogen; a linear or branched, saturated or unsaturated (C_1-C_8)-alkyl group, optionally substituted with (C_1-C_8)-alkoxy, carboxy, (C_1-C_8)-alcoxycarbonyl, amino, hydroxy, said amino and hydroxy being optionally (C_1-C_{22})-acylated or (C_1-C_{22})-alkylated; or a residue of an amino-acid;

and salts or solvates thereof.

2. Composition according to claim 1 wherein R^1 is a methyl, an ethyl, an isopropyl or a n-propyl group.

3. Composition according to claim 1 or 2 wherein R^2 is a methyl, an ethyl, an isopropyl or a n-propyl group.

4. Composition according to claim 1, in which the 3-hydroxy-4-pyridone is selected from the group consisting of

3-hydroxy-1,2-dimethyl-4-pyridone,

1-ethyl-3-hydroxy-2-methyl-4-pyridone,

1,2-diethyl-3-hydroxy-4-pyridone,

3-hydroxy-1-(2'-hydroxyethyl)-2-methyl-4-pyridone,

3-hydroxy-1-(2'-methoxyethyl)-2-methyl-4-pyridone,

3-hydroxy-1-methyl-2-pyridone,

1-ethyl-3-hydroxy-2-pyridone,

1,2-diethyl-3-hydroxy-2-pyridone,

3-hydroxy-4-pyrone,

3-hydroxy-2-pyrone,

3-hydroxy-2-methyl-4-pyrone,

3-hydroxy-2-ethyl-4-pyrone,

and salts thereof.

5. Composition according to any one of the preceding Claims, further comprising one or more esfoliating agent.

6. Composition according to Claim 5 wherein the esfoliating agent is an alpha hydroxy acid (AHA), salicylic acid or trichloroacetic acid.

7. Composition according to Claim 6 wherein the AHA is selected in the group consisting of glycolic acid, lactic acid, mandelic acid and mixture thereof.

8. Composition according to any of the preceding Claims, further comprising one or more additional depigmenting agent.

9. Composition according to the preceding Claim, wherein the depigmenting agent is selected in the group consisting of kojic acid; caffeic acid; retinoic

acid; hydroquinone and the derivatives thereof; ascorbic acid and the derivatives thereof; hydroxycinnamic and caffeic acids and esters thereof; benzofurans, extracts of plants and steroidal anti-inflammatory agents of hydrocortisone type.

10. Composition according to any of the preceding Claims, further comprising one or more anti-inflammatory agents.

11. Composition according to the preceding Claim, wherein the anti-inflammatory agent is selected from the group consisting of alphabisabolol, beta-glycyrrhetinic acid, allantoin, aloe extract, rosmarinic acid, azulene and derivatives thereof, asiaticoside, sericoside, ruscogenin, escin, escolin, quercetin, rutin, betulinic acid and derivatives thereof, catechin and derivatives thereof.

12. Composition according to any of the preceding Claims comprising 0.01 to 50% by weight of at least one compound of formula (I) or (II) optionally in admixture with suitable customary auxiliary agents.

13. Composition according to any of the preceding Claims comprising 0.1 to 20% by weight of at least one compound of formula (I) or (II) optionally in admixture with suitable customary auxiliary agents.

14. Composition according to any of the preceding Claims for the treatment of hyperpigmentation caused by either excessive melanogenesis and concomitant hemosiderinic deposits.

15. Use of a compound of formula (I) or (II) according to claim 1 for the treatment of hyperpigmented skin.

16. Use of a composition according to Claims 1 to 14 for the treatment of hyperpigmented skin.

17. A method of treatment of hyperpigmented skin which comprises administering an effective amount of a compound of formula (I) or (II) according to claim 1.

18. Method of treatment of hyperpigmented skin which comprises administering composition according to Claims 1 to 14.

19. Method according to Claims 17 or 18 wherein said composition is topically administered.

20. Method according to Claims 17 to 19 for the treatment of either excessive melanogenesis and/or hemosiderinic deposits.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/01275

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/48 A61K31/35 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2001	31/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fischer, J.P.

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INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/IB [redacted]01275

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[redacted]tion on patent family members

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